Fighting antibiotic resistance with carbohydrate-based inhibitors for lipopolysaccharide biosynthesis

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Antibiotic resistance is recognized as one of the greatest threats to human health and the need for new antibiotics is undisputed. Gram-negative bacteria are of great concern since there are today strains that are resistant to all approved drugs and are hence untreatable. It is thus necessary to find new targets and modes of action to fight bacterial infections to maintain antibiotic efficiency. In our research we target the virulence of the bacteria rather than the cell growth, a very attractive method, which minimize the risk for selection of a resistant mutant. We develop carbohydrate-based inhibitors for lipopolysaccharide (LPS) biosynthesis of Gram-negative bacteria with focus on the ADP-L-glycero-β-D-manno-heptose (ADP-L,D-Hep) biosynthesis. L,D-Hep is a conserved part of the inner core of LPS and the first carbohydrate that can be removed without hampering cell growth. However, without access to L,D-Hep the bacteria will produce a truncated LPS that will make the bacteria sensitive to external stresses, such as the immune system.